Long-Term Outcomes after Drug-Eluting Stent Implantation: Get Your Feet Wet in the Real-World

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The Reality and The World

The term "real-world" was coined in the early 1960s and refers to the realm of practical or actual experience, as opposed to an abstract, theoretical, virtual, or idealized world. In our everyday "real-world" practice, we not so rarely feel a tugging between evidence from some (idealized?) randomized controlled trials (RCT) and the clinical application of their results to the specific patient that we have in front of us. That is what several of our colleagues named the difference between "evidence-based" and "patient-based" medicine. In the practice of interventional cardiology, this feeling is even more manifest regarding the "first-generation" drug-eluting stents (DES)—namely, sirolimus (SES)- and paclitaxel (PES)-eluting stents. Without any doubt, these first DES revolutionized the intervention world by making it possible to treat millions of people worldwide *virtually perfectly*. "Virtually perfectly" because, as noticed since the end of 2003, the *reality* of the extended use of DES wowed the actual vulnerable DES Achilles heel: an increased occurrence of device-mediated myocardial infarction due to late stent thrombosis. You all know this story well and we will not reiterate the details. However, one should realize that this true complication was rare enough that RCTs—even those performed in all-comers—were clearly underpowered and had follow-up too soon after surgery to detect the problem.

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The Reality and the First-Generation DES

From the intense scrutiny initiated since the *2006 firestorm*,[1] we have learned more: First, that DES are associated with primary late stent thrombosis with a yearly incidence estimated at 0.5%.[2] Second, this is balanced against the reduced need for revascularization compared to bare metal stents (BMS). Third, the global safety profiles of first-generation DES are identical or even better than BMS with no difference in the overall risk of mortality. But finally, we learned something even more essential: Large real-world registries (such as the *Bern-Rotterdam*[2] or the *Dartmouth Hospital Dynamic Registry* published in this edition[3]) still belong to the current armamentarium of clinical research and that only trials with long-term follow-up are able to detect and circumscribe rare problems, such as late stent thrombosis.

Several RCTs directly compared the PES with the SES in all-comers, but few studies report a clinical follow-up of longer than 1 year. Only *Danish Organization on Randomized Trials With Clinical Outcome* (SORT-OUT II—2,098 patients, maximum follow-up: 18 months),[4] TAXi (202 patients, maximum follow-up: 36 months)[5] and *Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization* (SirTax—1,012 patients, maximum follow-up: 60 months)[6] have reported such extended follow-up

Table 1. Prospective, Open-Label, Randomized Clinical Trials (RCTs) Directly Comparing SES with PES

	Studies on CIN					Studies on SES/PES		
	ICON	VALOR	CARE	RECOVER	Feldkamp et al.	SORT-OUT II	TAXi	Dartmouth Hospital Dynamic Registry
Patient type	Chronic renal failure	Chronic renal failure	Chronic renal failure	Chronic renal failure	All-comers	All-comers	All-comers	All-comers
No. of patients	71/74	156/143	210/204	140/135	105/116	1,033/1,065	100/102	1012/1332
Diabetics	42%49%	52%/52%	44%/38%	34%/36%	40%/35%	13.9%/14.6%	36%/33%	28%/29%
%PCI	67%/65%	N.A.	39%/40%	44%/38%	N.A.	100%	100%	100%
Contrast media	Iodixanol/ Iopromid	Iodixanol/ Ioversol	Iodixanol/ Iopamidol	Iodixanol/ Ioxaglate	Iodixanol/ Ioxaglate	N.A.	N.A.	N.A.
Mean contrast use (mL)	215/204	118/130	136/134	205/195	N.A.	159/157	139 ± 13	304/311
CIN definition	SCr ↑ >0.5 mg/dL or >25%	SCr ↑ >0.5 mg/dL	SCr ↑ >0.5 mg/dL	SCr ↑ >0.5 mg/dL or >25%	SCr ↑ >25%	N.A.	N.A.	SCr ↑ >25%
Incidence of CIN (%)	16%/24%	22%/24%	4.4%/6.7%	8%/17%	7%/9%	N.A.	N.A.	13%/13%
Floroscopy time (minutes)	N.A.	N.A.	N.A.	N.A.	N.A.	6.5/6.5	9.4 ± 2.7	24.4/22.1
Reference	12	13	15	14	11	4	5	3

CIN = contrast-induced nephropathy; SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent; PCI = percutaneous coronary intervention.

results. As several millions of DES have been implanted worldwide since 2002 (real-world maximum follow-up of >8 years), trials with long-term outcomes are still warranted. In the present edition of the *Journal of Interventional Cardiology,* Brown, et al. focused on clinical outcomes up to 28 months in 2,362 consecutive patients treated with first-generation DES.[3]

This registry used modern statistical techniques and adjusted for nine different variables using a propensity score and modeling Cox's proportional hazard. The overall number of patients included in the present trial makes it the fifth largest registry directly comparing PES to SES worldwide after STENT,[7] *Evaluation of Drug Eluting Stents and Ischemic Events* (EVENT),[8] *Bern-Rotterdam,*[2] and *Western Denmark Heart Registry*[9] and the second most important within the United States. The study was performed at Dartmouth Hospital; Darthmouth Hospital was rated as one of the 30 best teaching hospitals in the United States, according to a study concerning 971 US cardiovascular centers carried out in 2009 by Thomson Reuters.[10]

What could we learn from this registry? Although the absolute values are too low to be convincing, it confirms that no statistically significant differences in clinical outcome can be found between patients treated with PES or SES (28-month mortality: PES, 4.7%; SES, 3.8%; $P < 0.05$). This is factual but not new; while most of the studies with early angiographic outcomes and some studies with clinical end-points during the first 12 months found advantages of SES over PES, all RCTs (*SORT-OUT, TAXi* and *SirTax*) with longer follow-up durations, and all registries except one (*Western Denmark Heart Registry*), demonstrated similar clinical outcomes between the two different DES.

Reality and The Intervention World

On the other hand, what is new—and more convincingly matches reality—is the occurrence of procedure-related complications. This is crucial but seldom disclosed information. The authors should be congratulated for their bravery. Due to patient and operator selection, complications are rare in RCTs. In retrospective registries, complications are usually underestimated. Only prospective registries can yield valid data regarding complications in the real world. The most important complication rates found in the *Dartmouth Hospital Dynamic Registry* were as follows: in-hospital mortality from 1.4–2%, periprocedural stroke rate from 0.6%, and—more interestingly—13.2–13.5% of

the patients developed a contrast-induced nephropathy (CIN, defined as an increase in the serum creatinine of $> 25\%$) with a 0.4–0.5% dialysis requirement. Is it much? Little evidence exists on this particular subject.

CIN is highly clinically relevant and is generally associated with patient and procedural characteristics, such as the presence of chronic renal failure, diabetes mellitus, or arterial hypertension, as well as the type and amount of contrast media infused. Table 1 summarized recent studies on the incidence of CIN after coronary angiography and PCI in RCT comparing different nonionic contrast-media and was balanced with the amount of nonionic contrast media injected in three different studies comparing PES to SES in unselected all-comers (*SORT-OUT II, TAXi* and *Dartmouth Hospital Dynamic Registry*). Based on studies comparing nonionic contrast media, the incidence of protocol-defined CIN occurred in 7–9% of all-comers[11] and 4–24% of patients with chronic renal failure.[12–15] In the presence of important differences between the studies (type, size,% of PCI), the comparison of these results with the *Dartmouth Hospital Dynamic Registry* could only be informative. Nevertheless, we should note that in comparison with the two others SES-PES trials that published the amount of injected contrast-media and the duration of fluoroscopy in all-comers, the PCI recorded in the *Dartmouth Hospital Dynamic Registry* appear dull: The amount of contrast used was two times higher and the duration of fluoroscopy about three times higher than the two others studies. What made these differences? Are they due to more complex patients or lesions? To operators' skills? To biases in the registry? We are not able to answer these questions, but the difference remains and should reinforce our quest to strive for optimal coronary result with minimal complication rates. Finally, we should also ask ourselves how real reflects the "real-world" described in the present registry to our reality?

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